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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/739,933	12/18/2000	James Steven Reid	90417X	4882

7590 03/28/2008

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EXAMINER	
MACFARLANE, STACEY NEE	
ART UNIT	PAPER NUMBER
1649	

MAIL DATE	DELIVERY MODE
03/28/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/739,933	REID ET AL.	
	Examiner	Art Unit	
	STACEY MACFARLANE	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-8,33,63 and 64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-8,33,63 and 64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 December 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/26/2002; 1/6/2003; 1/28/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 28, 2008 has been entered.

Response to Amendment

2. Claims 1, 2, 5, 33, and 63 have been amended as requested in the amendment filed on January 28, 2008. Following the amendment, claims 1, 2, 5-8, 33 and 63-64 are pending in the instant application and under examination in the instant office action.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 2, 5-8, 33 and 63-64 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 recites functional fragments of TGF-alpha. Claims 2, 5-8, 33 and 63-64 are dependent from Claim 1 and do not further limit the "functional fragments", and are therefore included in the rejection. The claims do not require that the ""functional fragments" possess any particular conserved structure or other disclosed distinguishing feature. Thus the claims are drawn to a genus of peptides defined only as functioning like TGF-alpha, therefore the genus is merely defined by function and the instant specification fails to describe the entire genus of molecules that are encompassed by these claims.

In making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, it is necessary to understand what Applicant has possession of and what Applicant is claiming. From the specification, it is unclear that Applicant is in possession of specific examples of "functional fragments" of TGF-alpha. The claims, however, encompass method of administration of "functional fragments", thus, the claims are not limited to specific molecules with known structure. The claims merely require the claimed methods employ molecules that function like TGF-alpha.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In the instant case, the only factor present in the claim is a

recitation of activity. There is not even identification of any particular portion of the structure that must be conserved for activity. The specification does not provide a complete structure of any functional fragment of TGF-alpha. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, the court clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the peptide structures of the encompassed genus of functional fragments of TGF-alpha, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of identifying activity. Adequate written description requires more than a mere recitation of activity as part of the invention and a reference to a potential method of isolating or screening. The compound itself is required. See *Fiers v Revel*, 25 USPQ2d 1601 at 1601 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to

be unpatentable due to lack of written description for that broad class. The specification only provided for the bovine sequence.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

5. Claims 1, 2, 5-8, 33 and 63-64 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for increasing neural progenitor cells or progeny thereof, at a site of damage within the striatum via intrastriatal infusion, does not reasonably provide enablement for the method for attracting neural progenitor cells to a site of CNS damage or lesion comprising parenterally administering TGF-alpha outside the ventricles. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1, 2, 5-8, 33 and 63-64 broadly encompass methods comprising parenterally administering TGF-alpha anywhere outside the ventricles wherein administering effects migration of the neural progenitor cell to any site of CNS damage or lesion. As Applicant has stated on pages 6-7 or Remarks filed January 28, 2008, Dorland's Illustrated Medical Dictionary recites a wide variety of parenteral types of administration, including subcutaneous, and intramuscular. The instant specification (¶ 0136) defines parenteral as "e.g., intravenous, intradermal, or intramuscular injection; oral administration; or direct application to the affected area". Thus, the claims are

broadly drawn to methods comprising administration of TGF-alpha by any of these modes and, in their broadest reasonable interpretation, read upon the effect of attracting a neural progenitor cell to any site of CNS damage or lesion by administration via any of these parenteral modes. Thus, the claims read upon methods comprising oral administration of TGF-alpha for attracting neural progenitor cells to a site of spinal cord injury. In this way, the claims encompass an unreasonably large scope of methods comprising a vast array of modes of administration in order to mediate effects at an unreasonably broad scope of CNS sites of damage.

The invention is based on the finding that intracerebroventricular and intrastriatal infusion of TGF-alpha leads to a large increase in the number of cells around the ventricle or striatal ridge, respectively, and that these cells demonstrate strong nestin immunoreactivity and lack immunostaining for glial markers. Further, the instant specification notes that by varying the location and dose of TGF-alpha infusion the site and number of cells involved could be controlled and concludes "The exact shape and apparent movement of the ridge depends on the site of the TGF-alpha infusion" (page 72, lines 6-19). Thus, the effects are largely confined to a localized effect, with the site of cellular incorporation dependent upon the site of TGF-alpha infusion. Additionally, it is noted that subsequent to infusion into the brain, systemically administered BrdU is incorporated solely into the subventricular zone within the first three days (page 72, lines 24-26) and subsequently BrdU cells are seen in the "ridge, striatum, external capsule and cortex adjacent to the infusion cannula" (*Id*, lines 26-27). This is taken to indicate further support for a localized effect and a lack of enabling disclosure as to how

one of ordinary skill in the art would perform the method of attracting neural progenitors to any site of damage, say for example to the spinal cord. Thus, the disclosure is not enabling for the use of the method of the invention commensurate with the broad scope of the claims.

As it is stated by Applicant on page 7 of Remarks filed January 28, 2008, at the time of filing and even currently, "[Applicant] is unaware of any FDA approved medicinal proteinaceous material that is to be taken orally for treatment of other than the gastrointestinal (GI) tract, let alone an orally administered peptide that is said to successfully pass through the GI tract and into the CNS, to ellicit a therapeutically effective response. It is submitted that human bodies are designed to prevent successful administration of such proteinaceous materials". Applicant concludes that one of ordinary skill in the art would not be able to accomplish successful oral administration of a peptide according to the method without a completely enabling description. Examiner agrees and finds that the instant specification provides neither enough guidance for such method, nor working examples, which would show that the claimed method was successfully achieved. Absent such guidance, one of ordinary skill in the art would require undue experimentation to discover how to practice Applicant's invention, as currently claimed.

The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative

skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. *In re Wands*, 8 USPQ2d, 1400 (CAFC 1988).

The nature of the invention relates to the in vivo attraction of a neural progenitor cell or progeny thereof to a site of CNS damage or lesion comprising parenterally administering, outside of the ventricles, purified TGF-alpha polypeptide or a functional fragment thereof.

The state of the art at the time of filing recognized that many neurotrophic factors protect striatal cells or reverse their degeneration within *in vivo* lesion models (Otto and Unsicker, J. Neuroscience, 10:1912-1921 1990; *abstract only*, Schmacher et al. Neuroscience, 45:561-570, 1991; *abstract only,* Venero et al. Neuroscience 61:257-268, 1994). However, each of these studies disclosed intrastriatal or intracerebral administration and localized neurotrophic effects, indicating that much unpredictability remained within the art with regard to other modes of administration. Furthermore, it was known in the art that TGF-alpha had specific in vitro effects on retinal epithelial cells and striatal dopaminergic neurons (*abstract only*, Anchan et al. *Neuron,* 6: 923-936, 1991; *abstract only*, Alexi and Hefti, *Neuroscience,* 55:903-918, 1993).

With respect to claim breadth, the standard under 35 U.S.C. §112, first paragraph, entails the determination of what the claims recite and what the claims mean as a whole. In addition, when analyzing the scope of enablement, the claims are analyzed with respect to the teachings of the specification and are to be given their broadest reasonable interpretation that is consistent with the specification. See MPEP 2111 [R-1], which states: "During patent examination, the pending claims must be

"given *>their< broadest reasonable interpretation consistent with the specification." *In re Hyatt*, 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000). Applicant always has the opportunity to amend the claims during prosecution, and broad interpretation by the examiner reduces the possibility that the claim, once issued, will be interpreted more broadly than is justified. *In re Prater*, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550- 51 (CCPA 1969)".

As such, the broadest reasonable interpretation of the claimed method is that it allows the attracting of a neural progenitor cell or progeny thereof to any site of damage or lesion in the CNS via parenteral (defined within the instant specification as "e.g., intravenous, intradermal, or intramuscular injection; oral administration; or direct application to the affected area") administration of a purified TGF-alpha polypeptide. Thus, the claims encompass an unreasonable number of distinct sites of damage within the CNS, many of which, like the spinal cord, have never demonstrated a nexus to or association with a population of neural progenitor cells. A skilled artisan would not know how to perform the method as broadly claimed based solely on a parenteral administration of TGF-alpha protein. As opposed to the claims, what is disclosed about the claimed method is narrow: The working examples provide guidance as to the intracerebroventricular (subsequently removed from the scope of the claims by a negative limitation) and intrastriatal infusion of TGF-alpha increases the number of putative neural progenitor cell in the ventricular or striatal regions, respectively. Therefore, the disclosure provides no guidance as to how to use the invention to the full extent of the scope claimed.

While the skill level in the art is high, the level of predictability is low. As stated above, the state of the art at the time of filing provided no enabling disclosure for the intravenous, intradermal, intramuscular injection or oral administration of a neurotrophic polypeptide and the successful therapeutic CNS response within *in vivo* lesion models.

Applicant's invention is predicated on the finding that, by varying the location and dose of TGF-alpha infusion, the site and number of cells attracted to the lesion could be controlled and that the shape and apparent movement of cells to the ridge depends on the site of the TGF-alpha infusion. Subsequent to TGF-alpha infusion into the brain, BrdU is incorporated solely into the subventricular zone, the striatal ridge, striatum, external capsule, and cortex adjacent to the infusion cannula. The specification also discloses that these BrdU cells are most likely neural progenitor cells based upon their immunoreactive profile (Table page 62).

The standard of an enabling disclosure is not the ability to make and test if the invention worked but one of the ability to make and use with a reasonable expectation of success. A patent is granted for a completed invention, not the general suggestion of an idea and how that idea might be developed into the claimed invention. In the decision of *Genentech, Inc, v. Novo Nordisk*, 42 USPQ 2d 1001, (CAFC 1997), the court held that:

> "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" and that "[t]ossing out the mere germ of an idea does not constitute enabling disclosure". The court further stated that "when there is no disclosure of any

specific starting material or of any of the conditions under which a process is to be carried out, undue experimentation is required; there is a failure to meet the enablement requirements that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art", "[i]t is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement".

The instant specification is not enabling because one cannot follow the guidance presented therein and practice the claimed method of attracting neural progenitor cells to any site of damage or lesion within the CNS comprising parenteral administration of TGF-alpha without first making a substantial inventive contribution.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

7. Claims 1, 2, 5-7, 33 and 63-64 are rejected under 35 U.S.C. 102(a) as being anticipated by Alexi et al., *Neuroscience*, 78(1):73-86, published February 27, 1997. Claims 1, 2, 5-8, 33 and 63-64 are drawn in part to a method for increasing neural progenitor cells or progeny thereof, at a site of damage within the striatum via intrastriatal infusion.

8. The Alexi prior art teaches administration of TGF-alpha to the striatum at the site of unilateral intrastriatal quinolinic acid lesion. The reference specifically teaches administration of purified recombinant human TGF-alpha (page 74, paragraph 2) by intrastriatal injection continuing for seven days post-lesion. Thus, the prior art teaches the limitations of the instant claims wherein they recite: “outside the ventricles”, “intrastriatal infusion”, wherein the CNS tissue is brain tissue, adjacent to the subependymal zone, and administration by continuous infusion.

9. While the Alexi prior art demonstrates a marked increase of cells upon TGF-alpha infusion (Figure 2D), Examiner asserts that the resulting increase in cell number upon TGF-alpha administration noted within the prior art is consistent with the findings of the present application. The reference does not specifically identify these cells as neural progenitor cells, however, absent evidence to the contrary and barring laboratory facilities within the USPTO, the effect of identical modes of administration of an identical polypeptide would lead to the inherent claimed effect of "migration of the neural progenitor cell or progeny thereof to the site".

MPEP § 2112 provides guidance as to the Examiner's burden of proof for a rejection of claims under 35 U.S.C. 102 or 103 based upon the express, implicit, and inherent disclosures of a prior art reference. The case law clearly states that something which is old does not become patentable upon the discovery of a new property.

> “[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art’s functioning, does not render the old

composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999).

Thus, the claiming of a new use, new function or unknown property that is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). Further, *In re Crish*, 393 F.3d 1253, 1258, 73 USPQ2d 1364, 1368 (Fed. Cir. 2004), the court held that the claimed promoter sequence obtained by sequencing a prior art plasmid that was not previously sequenced was anticipated by the prior art plasmid which necessarily possessed the same DNA sequence as the claimed oligonucleotides. The court stated that "just as the discovery of properties of a known material does not make it novel, the identification and characterization of a prior art material also does not make it novel." *Id.* In addition the court has held that there is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); see also *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention."); *Abbott Labs v. Geneva Pharms., Inc.*, 182 F.3d 1315, 1319, 51 USPQ2d 1307, 1310 (Fed.Cir.1999).

The case law specifically applies to the instant application where Applicant has claimed a method comprising administration of the TGF-alpha polypeptide in terms of a function, property or characteristic, and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference. In the instant case, Applicant's invention is directed to administrating purified TGF-alpha outside of the ventricles. The examiner has applied prior art which disclosed administration of purified recombinant human TGF-alpha by intrastriatal infusion. The examiner's assertion of inherency is based upon the structural similarity between the patented composition and the claimed composition and a mode of administration that identical with the claimed method.

Where the claimed and prior art methods use products and modes of administration that are identical or substantially identical, a *prima facie* case of either anticipation or obviousness has been established and the burden of proof rests upon the Applicant to demonstrate that the prior art does not necessarily or inherently possess the characteristics of Applicant's claimed product. *In re Fitzgerald*, 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977)). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

Conclusion

10. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STACEY MACFARLANE whose telephone number is (571)270-3057. The examiner can normally be reached on M,W and ALT. F 6 am to 3 pm, T & R 5:30 am - 4 pm..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Stacey MacFarlane
Examiner
Art Unit 1649

/John D. Ulm/
Primary Examiner, Art Unit 1649